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(54) Title: PARENTERAL PHARMACEUTICAL COMPOSITIONS CONTAINING GF120918A

(57) Abstract

Pharmaceutical compositions that prevent or minimize precipitation upon injection or infusion, comprising: a) a safe and therapeutically effective amount of *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide and its physiologically acceptable salts and solvates; b) a safe and effective amount of a surfactant; c) a buffer system; and d) a pharmaceutically acceptable carrier.

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PARENTERAL PHARMACEUTICAL COMPOSITIONS CONTAINING GF120918A

FIELD OF THE INVENTION

The present Invention relates to novel pharmaceutical compositions that are useful in preventing malignant cells from becoming resistant to a diverse variety of chemotherapeutic agents.

BACKGROUND OF THE INVENTION

The multidrug-resistance inhibitor, chemically known as *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide and its physiologically acceptable salts and solvates is described and claimed in World Patent Application WO 92/12132, filed in the name of Laboratires Glaxo S.A. and published July 23, 1992. Multidrug-resistance is a process whereby tumor cells become resistant to structurally diverse chemotherapeutic agents following exposure to treatment with anti-tumor drugs. This acquired drug resistance can be a major obstacle in the clinical treatment and management of malignant disease. It has been shown that this type of resistance can be reversed by GF120918, resensitizing multidrug-resistant tumor cells to various chemotherapeutic agents. It has also been seen that certain tumors are intrinsically multidrug-resistant and the use of multidrug-resistance inhibitors are also beneficial in treating tumors of this type.

GF120918A, the hydrochloride salt of *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide, to be safely and effectively administered to patients parenterally by either intravenous injection or intravenous infusion must be adequately miscible in the blood. Therefore, any combination of the drug and the various excipients, in a liquid form, must be sufficiently compatible with the physiological composition of the blood to allow sufficient admixing. This mixing with the blood allows the compound to be distributed throughout the body in an unremarkable fashion. However, problems exist with the parental administration of GF120918A due to the compounds poor solubility. GF120918A is a weak base and therefore exhibits a higher solubility at a pH less than about 4. Since the pH of the blood is approximately 7.4, the compound alone in solution precipitates upon injection or infusion into the blood stream.

An object of the present Invention is to provide a parenteral formulation that when injected or infused into the blood stream remains miscible and allows

the active drug to be distributed throughout the body in an unremarkable fashion. A further object of the present Invention is to provide a parenteral formulation and method of use that will improve or increase the efficacy of a chemotherapeutic agent or restore sensitivity of a tumor to chemotherapeutic agent or reverse or reduce resistance of a tumor to a chemotherapeutic agent; subsequently abating tumor cell multidrug-resistance and decreasing morbidity.

Publications such as *In Vitro* Method for Detecting Precipitation of Parenteral Formulations After Injections, Journal of Pharmaceutical Sciences, Vol. 72, No. 9, September 1983; Pluronic Surfactants Affecting Diazepam Solubility, Compatibility, and Adsorption From i.v. Admixture Solutions, Journal of Surface Sciences, Vol. 11, No. 4, 1988, Taiwan, Republic of China, Precipitation of the Renin Inhibitor Ditekiren Upon iv Infusion: *in Vitro* Studies and Their Relationship to *in Vivo* Precipitation in the Cynomolgus Monkey, Pharmaceutical Research, Vol. 8, No. 1, 1991; Intravenous premedication with diazepam. A comparison between two vehicles, Anesthesia, 1984, Vol. 39, p. 879-882; Precipitation of Solubilized Drugs due to Injection or Dilution, Drug Intelligence and Clinical Pharmacy, Vol. 11, July 77; and U.S. Patents 4,205,089 and 4,296,131, issued May 27, 1980 and October 20, 1981 both to Ladage et al., teach how to increase the solubility of a compound in a formulation. These publications advocate the use of: cosolvents, complexing agents, hydrotropic agents, liposomes, fat emulsions, polyaphrons, dimethylsulfoxide and surfactants. However, even though GF120918A is soluble in the standardized formulations utilized for parenteral administration, precipitation nevertheless occurs upon injection or infusion into the blood stream. This precipitation on infusion occurs as the formulation, a weak base, mixes within the pH neutral blood stream. The novel compositions of the present Invention maintain solubility within the blood stream and prevent precipitation of the drug upon injection or infusion into the blood stream.

SUMMARY OF THE INVENTION

The present Invention relates to pharmaceutical compositions that prevent or minimize precipitation upon injection or infusion; comprising:

a) a safe and therapeutically effective amount of *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide and its physiologically acceptable salts and solvates;

b) a safe and effective amount of a surfactant;

c) a buffer; and

d) a pharmaceutically acceptable carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

By "safe and therapeutically effective amount," as used herein, means a sufficient amount of a drug or pharmaceutical agent to abate or reverse a multidrug-resistance response of a tissue, system or animal that is being sought by the researcher or clinician without harming the tissues of a mammal, including a human to which the drug is administered.

The compositions of the present Invention employ a safe and therapeutically effective amount of the compound *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide (GF120918) and its physiologically acceptable salts and solvates, a safe and effective amount of a surfactant, a safe and effective amount of a buffer and a carrier or diluent suitable for pharmaceutical use. These compositions are suitable for administration to mammals, including humans through various parenteral routes. These various parenteral routes particularly include both intravenous bolus injection and intravenous infusion.

Persons who treat cancer and other diseases which become resistant to chemotherapeutic, anti-tumor compounds would use the compositions of the present Invention to resensitize multidrug-resistant cells to chemotherapeutic agents thus abating multidrug-resistance. Therefore, compositions of the present Invention may be administered in conjunction with an antitumor drug. Examples of suitable antitumor drugs for use in conjunction with compositions of the present include, but are not limited to, Vinca alkaloids (e.g. vincristine, vinblastine and vinorelbine, anthracyclines (e.g. daunorubincin, doxorubicin and aclarubincin, taxol, and derivatives thereof (e.g. taxotere), podophyllotixins (e.g. etoposide and VP16), mitoxantrone, actinomycin, colchicine, gramidine D, cisplatin, cyclophosphamide, amsacrine or any other chemotherapeutic, antitumor type compounds.

Compositions of the present Invention while being given in conjunction with an antitumor drug, could also be given simultaneously with an anti-tumor drug. This type of administration is acceptable as long as the components of the composition of the present Invention and any antitumor compound given simultaneously are both physically and chemically compatible. In this instance

"simultaneously" means, sequentially with little or no delay or given together from a common single container where the composition of the present Invention and th antitumor drug are physically mixed.

The medical community, particularly oncologists and other medical professionals who treat persons afflicted with tumor disease recognize that patients suffer various adverse side-effects from the administration of chemotherapeutic anti-tumor drugs. One of the most serious side effects produced by chemotherapeutic anti-tumor drugs is nausea and vomiting. Nausea and vomiting can result in severe consequences leading to increased morbidity and mortality. Compositions of the present Invention may also be administered with various drug formulations to combat side-effects produced by anti-tumor chemotherapy. These other drug formulations may be given either simultaneously or in conjunction with formulations of the present Invention. If given simultaneously by either being admixed in the same syringe for injection or admixed in the same intravenous bag or bottle for infusion the various formulations must be both physically and chemically compatible with compositions of the present Invention. If, however, the formulation given in conjunction with compositions of the present Invention or given together at the same time, but from a different container or is given by another route or given intravenously either prior to or subsequently to compositions of the present Invention physical and chemical reactivity should not be problematic.

Parenteral compositions of the present Invention must be in a sterile form. Any of the various methods known to persons skilled in the art employed to prepare sterile parenteral preparations that will not degrade components of the present Invention are suitable for use in the compositions sterile preparation. Parenteral compositions of the present Invention may be packaged, produced or contained in packaging materials such as single use ampoules, vials or intravenous bottles or bags or alternatively in multidose or multiuse vials or containers.

Compositions of the present Invention may also be packaged as articles of manufacture comprising a safe and therapeutically effective amount of GF120918 and its physiologically acceptable salts and solvates; a safe and effective amount of a surfactant; a buffer; and a pharmaceutically acceptable carrier or diluent, packaged as described above. The packaging material may also have labeling and information relating to the pharmaceutical composition printed thereon.

Additi nally an article of manufacture may have a brochure, report, notice, pamphlet, or leaflet containing product information. This form of pharmaceutical product information is sometimes, in the pharmaceutical industry, called the "package insert." A package insert may be attached to or included with a pharmaceutical article of manufacture. The package insert and any article of manufacture labeling provides information relating to the pharmaceutical composition. This information and labeling provides various forms of information utilized by health care professionals and patients that describes the composition, its dosage and various other parameters required by regulatory agencies, such as the United States Food and Drug Administration.

The pH of the present compositions range from about 1 to about 5, particularly from about 2.5 to about 4. The essential, as well as possible optional components of the compositions of the present Invention, are described in the following paragraphs.

Essential Components

One of the essential components of the present Invention is GF120918 and its physiologically acceptable salts and solvates, described in International Patent Application WO 92/12132, published 23 July 1992. GF120918 is an acridine derivative that is able to reverse or reduce resistance to, increase or restore sensitivity to or improve or increase the efficacy of an chemotherapeutic agent or agents.

The amount of GF120918 administered to prevent, abate or reverse multidrug resistance in a mammal including a human will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of about 1 mg to about 10 gm per day, particularly from about 10 mg to about 1 gm per day and more particularly from about 25 mg to about 750 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

Another of the essential components of by the present Invention is a surface-active agent or a mixture of compatible surface-active agents, sometimes referred to as surfactants. Any compatible surface-active agent is sufficient for use

in the present Invention, however, nonionic surface-active agents are particularly suitable.

Nonionic surface-active agents are particularly suitable in compositions of the present Invention and can be broadly defined as compounds produced by the condensation of alkylene oxide groups (hydrophilic in nature) with an organic hydrophobic compound which may be aliphatic or alkylaromatic in nature. Examples of suitable nonionic surfactants include, but are not limited to: pluronics, polyethylene oxide condensates of alkyl phenols, products derived from the condensation of ethylene oxide with the reaction product of propylene oxide and ethylene diamine, ethylene oxide condensates of aliphatic alcohol's, long chain tertiary amine oxides, long chain tertiary phosphine oxides, long chain dialkyl sulfoxides and mixtures of such materials.

The surface-active agent or mixtures of compatible surface-active agents can be present in the compositions of the present Invention from about 0.05% to about 20.0%, particularly from about 0.1% to about 10.0% and most particularly from about 0.5% to about 5.0% by weight of the total composition.

The surface-active agents best suited for inclusion into the present composition are: polyethylene glycol 660 hydroxystearate (SOLUTOL® HS-15), polyoxyethylene castor oil derivatives (CREMOPHOR® EL, RH40, and RH60), poloxamer, polyoxyethylene alkyl ethers (CETOMACROGOL® 1000) and polyoxyethylene sorbitan fatty acid esters (POLYSORBATE® 20, 40, 60, and 80 and TWEEN® 20, 40, 60 and 80). In particular polyethylene glycol 660 hydroxystearate, polyethylene glycol, polyoxyethylene castor oil derivatives and polyoxyethylene sorbitan fatty acid esters are useful in compositions of the present Invention.

Another essential component of the present Invention is a buffer or mixture of buffers. Buffers are compounds or mixtures of compounds which if present in a solution resist changes in the pH of the solution upon the addition of small quantities of acids or bases. Further information about buffers can be found in Remington's Pharmaceutical Sciences, p. 243 - 45 17th ed. (1985). Examples of buffers suitable for use in compositions of the present Invention include: acetate, phosphate and glutamate.

The last essential component of the present Invention is a suitable carrier or diluent that provides an appropriate vehicle for parenteral delivery of the

composition without the introduction of untoward side-effects. Persons skilled in the art will quickly realize that any carrier or diluent intended for parenteral administration that is compatible with the essential and any optional components of the present Invention will be suitable. Examples of suitable carriers and diluents include, but are not limited to: dextrose 5% in water and sterile water for injection.

Optional Components

In addition to the above described essential components, the compositions of the present Invention can contain a variety of optional parenteral conventional components known to persons skilled in the art. Any optional components included in compositions of the present Invention must be physically and chemically compatible with the essential components of the present Invention. Optional components include, but are not limited to: cosolvents, including but not limited to, polyethylene glycol (PEG) grades 200 to 600, propylene glycol (1,2-propanediol), ethanol and glycerin, preservatives and agents that adjust isotonicity and osmolality. Further information concerning preservatives and agents to adjust isotonicity and osmolality can be found in Remington's Pharmaceutical Sciences, p. 1278 - 1280, 1455 - 1472, 17th ed. (1985)

Optional components may also include other drugs or combinations of drugs that are physically and chemically compatible with compositions of the present Invention. Possible optional additional drugs include, but are not limited to antitumor chemotherapeutic agents, antinausents including, serotonin 5-HT_3 receptor antagonists such as ondansetron and granisetron and various other antinausents such as prochlorperazine, chlorpromazine, perphenazine, thiethylperazine, trifluprornazine, droperidol, methochlopramide, trimethobenzamide, dronabinol, pherergan, nabilone and methylprednisone. Other additional optional drugs include: antibiotics, antidepressants, antiulcer compounds, analgesics, anticholornergics, antivirals and a myriad of other drugs suitable to treat conditions that also require the administration of compositions of the present Invention.

METHOD OF MANUFACTURE

The compositions of the present Invention can be made using methods and techniques that are commonly employed in preparing parenteral preparations within the pharmaceutical industry. Remington's Pharmaceutical Sciences, p. 1518 - 1541, 17th ed. (1985).

COMPOSITION USE

Compositions of the present Invention in their method aspect involves administering to a mammal, including a human a safe and effective amount of the compositions of the present Invention described herein. These safe and effective amounts will vary based on the type and size of mammal being treated and the results wished to be obtained.

EXAMPLES

The following examples further describe and demonstrate particular embodiments within the scope of the present Invention. The examples are given solely for illustration and are not to be construed as limitations as many variations are possible without departing from the Invention's spirit and scope.

Example I

Ingredients	Amounts
GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
TWEEN 80®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

Preparation

100 mL of 0.5 mg GF120918A/mL Intravenous Infusion, 0.05M Acetate, pH 3.75, 1% v/v TWEEN 80, qs with 5% Dextrose in water.

Pipette 286.5 µL of glacial acetic acid into a beaker and add approximately 50 mL of D5W. Weigh 1.08 g of polysorbate 80 and add to the beaker with glacial acetic acid and D5W. Using a spatula and rinsing with D5W if necessary, disperse the polysorbate 80 by stirring. Weigh 53.2 mg of GF120918A and dissolve it in the above solution. Add additional D5W until a total volume of approximately 98 mL is achieved. Dissolve 5 g of sodium hydroxide in 30 mL of distilled, deionized water in a separate beaker. Add the sodium hydroxide solution dropwise with stirring to the solution until a pH of 3.75 is achieved. Pour the resulting solution into a 100 mL volumetric flask and q.s. to 100 mL with D5W. Stir or shake the solution to ensure homogeneity. Filter the final solution through a 0.22 µ filter to ensure sterility.

Example II

GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
CREMOPHOR EL®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

Example III

GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
CREMOPHOR RH40®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

Example IV

GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
CREMOPHOR RH60®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

Example V

GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
SOLUTOL HS-15®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

Example VI

GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
TWEEN 60®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

Example VII

GF120918A	3.19 mg
PEG 300	0.4 mL
TWEEN 80®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example VIII

GF120918A	3.19 mg
PEG 300	0.4 mL
CREMOPHOR EL®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example IX

GF120918A	3.19 mg
PEG 300	0.4 mL
TWEEN 60®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example X

GF120918A	3.19 mg
PEG 300	0.4 mL
CREMOPHOR RH40®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example XI

GF120918A	3.19 mg
PEG 300	0.4 mL
CREMOPHOR RH60®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example XII

GF120918A	3.19 mg
PEG 300	0.4 mL
SOLUTOL HS-15®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example XIII

GF120918A	3.19 mg
PEG 300	0.4 mL
TWEEN 20®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example XIV

GF120918A	3.19 mg
PEG 300	0.4 mL
TWEEN 40®	100 microliters
Glacial acetic acid	17.2 microliters
Sodium Hydroxide	adjust to pH 3.5
Water for Injection (USP)	qs to 1 mL

Example XV

GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
TWEEN 20®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

Example XVI

GF120918A	0.53 mg
Glacial acetic acid	2.87 microliters
TWEEN 40®	10 microliters
Sodium Hydroxide	adjust to pH 3.75
5% Dextrose in water (USP)	qs to 1 mL

What is Claimed is:

1. A pharmaceutical composition that prevents or minimizes precipitation of the compositions active ingredient upon parenteral administration; comprising:

a) a safe and effective amount of *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide and its physiologically acceptable salts and solvates ;

b) a safe and effective amount of a surfactant;

c) a buffer; and

d) a pharmaceutically acceptable carrier or diluent.

2. A pharmaceutical composition according to Claim 1 wherein the pH is from about 1 to about 5.

3. A pharmaceutical composition according to Claim 2 wherein the amount of *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide or its physiologically acceptable, salts and solvates is from about 1 mg to about 10 gm.

4. A pharmaceutical composition according to Claim 3 wherein the surfactant is selected from the group consisting of: polyethylene glycol 660 hydroxystearate, polyoxyethylene castor oil derivatives, poloxamer, polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, polyethylene glycol, propylene glycol, ethanol and glycerin.

5. A pharmaceutical composition according to Claim 4 wherein the amount of surfactant is from about 0.5% to about 5%.

6. A pharmaceutical composition according to Claim 5 wherein the buffer is selected from the group consisting of: acetate, phosphate and glutamate.

7. A pharmaceutical composition according to Claim 6 wherein the amount of the buffer is from about 0.005% to about 0.5%.

8. A pharmaceutical composition according to Claim 7 wherein the pharmaceutically acceptable carrier or diluent is a sterile solution suitable for parenteral administration, selected from the group consisting of: dextrose 5% in water or sterile water for injection.

9. A pharmaceutical composition according to Claim 1 containing an additional buffer.

10. A pharmaceutical composition according to Claim 9 wherein the additional buffer is selected from the group consisting of: acetate, phosphate and glutamate.

11. A pharmaceutical composition according to Claim 1 additionally containing a safe and effective amount of a cosolvent.

12. A pharmaceutical composition according to Claim 11 wherein the cosolvent is selected from the group consisting of: polyethylene glycol, propylene glycol (1,2-propanediol), ethanol and glycerin.

13. A pharmaceutical composition according to Claim 1 additionally containing a safe and effective amount of and additional drug substance.

14. A pharmaceutical composition according to Claim 13 wherein the safe and effective amount of the additional drug substance is selected from the group consisting of: antinausents, antibiotics, antidepressants, antiulcer compounds, analgesics, anticholornergics and antivirals.

15. A pharmaceutical composition according to Claim 14 wherein the safe and effective amount of the additional drug substance is an antinausent selected from the group consisting of: serotonin 5-HT3 receptor antagonists, prochlorperazine, chlorpromazine, perphenazine, thiethylperazine, trifluprornazine, droperidol, methochlopramide, trimethobenzamide, dronabinol, pherergan, nabilone and methylpredinisone.

16. A pharmaceutical composition according to Claim 15 wherein the safe and effective amount of the additional drug substance is a serotonin 5-HT3 receptor antagonist.

17. A method of reversing, reducing or inhibiting multidrug-resistance or increasing or restoring sensitivity to a tumor by administering a safe and effective amount of a composition according to Claim 1.

18. A method according to Claim 18 wherein the composition is administered as a parenteral injection or parenteral infusion.

19. An article of manufacture comprising:

a) packaging material; and

b) a pharmaceutical composition contained within the packaging material, wherein the pharmaceutical composition prevents or minimizes

precipitation of the compositions active ingredient upon injection or infusion, comprising:

i) a safe and therapeutically effective amount of *N*-{4-[2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl}-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide and its physiologically acceptable salts and solvates;

ii) a safe and effective amount of a surfactant;

iii) a buffer; and

iv) a pharmaceutically acceptable carrier or diluent.

20. An article of manufacture of Claim 19 additionally comprising: a brochure containing product information.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/12952

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47 A61K47/10 A61K47/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHARM. RES., vol. 11, no. 10, 1 October 1994 NEW YORK LONDON, page 5269 XP 000566180 TONG W. ET AL 'Solubility behavior of GF120918A' see the whole document ---	1,2,4,6, 17-20
A	CANCER RES., vol. 53, no. 19, 1 October 1993 pages 4595-4602, XP 000565696 HYAFIL F. ET AL 'In vitro and in vivo reversal of multidrug resistance by GF120918, an acridonecarboxamide derivative' see page 4596, column 1, paragraph 5 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 March 1996	26.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Boulois, D

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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